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BREAKOUT SESSION B

BIOLOGICAL CHARACTERIZATION AND IMPURITIES

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P A R T I C I P A N T S

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P R O C E E D I N G S

MS. BROWN: Welcome to the Biological Characterization and Impurities Breakout Session. This breakout session is really a forum for all of you to come and share your ideas and engage in a scientific discussion about the biological characterization for follow-on protein products.

But let me first give you an introduction. We have three moderators, myself, Janice Brown; Inger Mollerup from Novo; Robin Thorpe from NIBSC; Steve Kozlowski from CDER; and Christopher Joneckis from CBER. Both Inger and Robin will be doing a brief five-minute presentation. I'm going to turn it over to them, and then later we'll discuss some of the guidelines for the workshop.

DR. THORPE: Thanks for that introduction, and I was really going to try and be very brief. And I'm not going to attempt to answer the question because I don't think that is the idea of these sessions. I think it's up to you and perhaps in the discussion. But all I was going to do in the five minutes was just talk about two issues which I

am familiar with which relate in some ways to the first two questions. I'm not going to get on to the third question at all, and I should state before I start, what I say is very much my opinion. It's not necessarily anybody else's opinion, and I'm sure at least some of you in the audience will disagree. So I'm hoping to be slightly provocative.

I also should say that I don't work for an innovator company or a follow-on company, and I only advise on regulatory matters so I'm pretty independent. So I've got no bias. I'm simply dealing with the scientific issues. What I'm going to talk about basically relates to this single slide that I'm going to use, and it's divided into two different topics.

Firstly, I was going to talk about bioassays, in particular the need for clinical relevance or lack of it and what are really required for bioassays, and this would apply equally I think to innovator type products and follow-ons. I think the thing to really remember

about bioassays is that you need to select them very much depending on what you're going to use them for, what is the purpose, and particularly what are you going to use the data that you generate.

And I think for most biologicals, you probably need during product development more than one assay. Precise number that you need depends on the product, but you certainly would probably need more than one. But you're also very likely to need different assays at different stages in product identification, development, and then finally for things like lot release and stability assessments.

And there are good reasons for that. You can imagine a situation where you might start off with developing a product, and you want to use biological assays or biological systems, and here I'm talking about animal systems as well as in vitro approaches, but basically what you'll be doing is doing the procedures to try and characterize the biological properties of your material, and you might like to try and find some

assays that give you some kind of ability to see how the material might perform clinically.

And that would really be the driving force behind the assay selection. You might not need super-robust, very precise, sensitive assays because you're not going to be using the assays for those sorts of things. You really are trying to use them for characterization. And I think this is the way most product development has gone with biologicals over the past several decades.

Having said that, I don't think you can use a bioassay as a surrogate for a clinical trial. You might get pointers from bioassay data, but in the end if you really want to assess clinical efficacy, you're going to have to rely on clinical trial data. Now whether you do the trial or whether you rely on somebody else's trial or you do an abbreviated trial, I think that's a different issue, but you certainly won't be able to rely exclusively on a bioassay for predicting clinical efficacy, and there are good examples, I think, quite well-known examples, where bioassay data,

even quite sophisticated multiple bioassay data, has suggested products would be very good in the clinic, but they have failed when they've actually been tried in humans.

If you think about experience with monoclonal antibodies and binding proteins for LPS, which can be shown to be very, very good in animal models, in bioassays, but they don't seem to perform so well when you get to the real clinical situation.

So I think there are loads and loads of examples like that in the literature, and if you think of the fail rate with biologicals that appear to be really good when you start out, but turn out to fail at the clinical stage, I think this is a very common finding. So you're not going to be able to get away with using bioassays as a kind of surrogate for clinical trials.

Having assumed eventually you have got an authorization to sell your product, a license, whatever it's called--it's called different things in different parts of the world--then I think you

really need to be using bioassays for different things. You need to certainly be using them for lot release to show batch-to-batch consistency in a lot of cases, not for all products, but certainly for some, the more complex, particularly the more complex biologicals.

And for that purpose, you probably don't really need clinical relevance because you've presumably already done the trial or relied on somebody else's trial to show that you have clinical efficacy. You're not using the bioassay to prove that yet again even if you could. And I think the important thing to remember at this stage is that you really need a good assay for lot release, showing batch-to-batch consistency and perhaps stability.

And this might be a quite different type of bioassay to those used earlier on in product development because here you want robustness, good, very good precision, perhaps high throughput and things like that, so you've different requirements because you're using the assays for different

purposes.

So what I think is the overall message is you need different bioassays for different purposes at different stages in product development, and you can't use them, at least directly, as a surrogate for clinical trials.

And I think if you look in the literature, and certainly I know that there are a quite a lot of biologicals that are controlled from the lot release perspective with assays that don't really seem to relate at all to their clinical use. A classic example would be gamma interferon controlled with antiviral assays or reporter gene assays when it's used as an antineoplastic or to control the other kinds of cell replication problems, and perhaps an even better example is beta interferon used to treat multiple sclerosis patients which is controlled with antiviral assays or other kinds of assays.

So there is plenty of precedent for this kind of thing in the literature and these kind of things are becoming more and more frequent. All

right. So that was all I was going to say about bioassays.

I'll move on to the reference preparation standards kind of question. It's certainly the case for any biological or most biologicals at least that you need reference preparations or reference standards. And that's because many of the assays are comparative so you have to compare your product to something, and usually that's some kind of reference standard.

Now, for many products, official type standards such as WHO standards or Pharmacopeia standards don't actually exist. So if you're in this sort of situation, you have to find something else to stand in for them, and either you make your own or you find another source. But in other cases, perhaps in the more established biologicals, there are what might be called higher purpose standards such as WHO international standards, pharmacopeia standards, and assay performance indicator type standards. And these can be very useful.

Again, as for the bioassays, I think the thing to remember is that you need standards for particular purposes, and many of these standards

are not sort of all encompassing. They are intended for a particular uses. WHO standards are very often intended for the calibration and validation of bioassays, and they're not really useful for many other purposes.

They often are not based on any licensed product. They're just based on a biological substance with a defined potency. So you can't use them as any kind of indicator of an ideal product. They're almost never that type of preparation and you have to remember that.

So it's basically again standards and reference preparations for intended purposes. You obviously have to use reference preparations for a whole range of different analytical procedures and with follow-ons, it's quite often difficult because you don't actually necessarily have access to the reference preparations that you want. And there seems to be a tendency at least in some

circumstances to try and purify or enrich or isolate active principles from existing standards, taking them out of their background formulation and perhaps concentrating them and trying to use them for all sorts of reference preparation purposes.

And in many cases, this does seem to work, at least to some extent, but you do have to remember there is a significant problem that the purification or isolation process might change the substance. So you might not actually have at the end of the exercise what you want or what you think you've got.

Another problem I've actually seen a real example is purification of a material present in very small amounts from a kind of reference preparation format, purification away from the excipient, which resulted in instability and actually considerable loss of material because basically the formulation has been removed, it's no longer stable, and it sticks to everything. So you have to be careful again if you're going to go that way.

That was all I was really going to say about reference preparations. I was going to deal with the last bit on this slide, how to deal with

variations in batches with follow-ons and innovators, but it was dealt with this morning by a colleague, so I don't think I'll bother to say anything about that because it was dealt with much better than I would do that. That's not to say that it's not very important.

Okay. It's over five minutes. Sorry. Okay. Thank you.

DR. MOLLERUP: I'll try to move on, again talking a little bit about other aspects of biological characterizations and basically also trying to ask questions maybe rather than provide direct answers, but basically taking a start looking at the whole spectrum of biological characterization methods and raising the discussion which ones you would find not needed for a follow-on biologic and how you would make that decision.

I think the talks this morning emphasized

in great detail the need for a thorough characterization, both chemical, physical chemical, protein chemical and biological, so I guess from my angle, it's sort of hard to find good reasons for not looking into these kinds of biological characterization data both because you need them to actually move your product onto the market, but certainly also because you will need them at the end of the day when the product is potentially on the market to manage process changes and what have you, and some of the assays, biological characterization in the sense that might be relevant at least at the end, that Robin just dealt with, in vivo models of efficacy and PK/PD. That was also discussed in very much detail this morning.

Mechanism of action. That was also covered, and receptor binding or, any other, I mean there's a lot of different binding studies that one can perform and again, of course, those decisions would be related to exactly what kind of product you are developing.

There are some other issues beside choosing the appropriate package of biological characterization. And there are some other issues

that are also highly relevant. One, moving to the next slide here, is formulation because in many cases there will be differences in the formulations. They may not be huge, but they may certainly be significant, and that will lead to the whole question popping up of what are your impurity profiles not only at product release but also at end of shelf life, and how are you going to characterize that and make sure that you know the product also had shelf life.

And in some of the same ball game, looking at risk management, we also discussed this morning what risks are we capable of assessing with our biological characterization methods, what residual risks could we identify, and I guess from my experience, some of those risks that certainly are out there are related to the fact that these biological manufacturing processes are so unique as they are starting from cell line, fermentation

processes, downstream processing, analytical characterization, what have you. And that will lead to some differences, again, in the impurity profile.

And moving back to what that means, I think that was also clear this morning that there is no way where we can characterize each and every impurity --we can't pull out all the necessary information of the physical/chemical characterization methods. In other words, we do need to add on some biological characterization data, and at the end of the day some clinical data to make sure that we are there.

And I think a final, an additional challenge here is that whereas the innovator has had various qualities, various quality characteristics, quality attributes of the products that were put into pre-clinical and clinical characterization, that at the end of the day have been part of establishing sort of your whole license to operate, that's not directly applicable for a follow-on unless you go through that same

pathway, and I think that also raises some additional questions, and I'm sure that quite a few of them will pop up, also based on the list of questions that we have put together for this session.

MS. BROWN: Okay. I would like to maybe go over some guidelines so when you actually come up and talk, if you could keep your discussions simply related to the biological characterization and not really address regulatory or legal issues. The FDA moderators and the facilitators here are just to facilitate discussion and to document some of the major points and not present our ideas.

Because all of our discussions and your comments are going to be transcribed, if you could clearly state your name along with your affiliation. The discussion should be really data driven; hard copies of any references or data should be submitted to the public docket. I think Keith actually presented the public docket and we'll do that at the end of the conference again. And during your comments, if you could include any

relevant examples, I think that would be really helpful.

Your individual comment should be limited to two or three minutes, and we may actually ask specific questions related to your comments to provide any type of clarification.

The important issues and points will be identified and recorded where consensus is reached and along where consensus is not reached. Dr. Joneckis is actually going to present and post it up there--maybe we can make it a little bit bigger so we can read it--and if you find that something is written inaccurately, if you come up and notify us, but you've got the three questions that we've put in the DIA brochure.

Chris is going to load them up. But let me summarize them. How can the clinical relevance of functional biological characterization studies be established?

And under that is under what circumstances can biological characterization studies be predictive of efficacy in humans and can this be

used to justify limited clinical studies, clinical efficacy studies?

We'll welcome any comments from the floor.

DR. NASHABEH: This is Wassim Nashabeh from Genentech. I'd like actually to second the point that Robin has mentioned earlier. If biological characterization is predictive of clinical efficacy, then 80 percent or so of drugs and clinical development would not have failed. They're basically a clinical endpoint. The biological characterization looked at best at one potential mechanism action or more of the drug itself, but may not represent the full function that the molecule can actually present eventually, and only in cases where there is a validated surrogate clinical endpoint that one can rely on such assays to actually predict clinical endpoint which at least in the history of all the products that we have, we have never had a correlation between a biological assay and a clinical endpoint.

MS. BROWN: Could you comment on whether you feel that a panel of bioassays, for example,

you can start with a binding assay, then an activity assay and then move on to an animal assay, and if you had a surrogate biomarker that could be correlated to a PD parameter in a clinical efficacy study or a clinical PD study for humans?

DR. NASHABEH: Going back to your point, the majority of these assays are already done in research phases prior to take a product into clinical development. So I think the biological assays and the biological characterization is quite powerful to give confidence in taking a product and moving it in clinical development to eventually establish its clinical efficacy, and then eventually towards the end of the clinical development, they serve a very good element or point of actually follow-up in terms of ensuring consistency of production from lot to lot, but at no point they replace basically a clinical endpoint.

Now, if there is a clinical surrogate, that can be cross-validated, then you can actually get some benefit of if you can cross-validate a

clinical surrogate to a biological endpoint, but that would be unusual. I'm not aware of an example where this is a case.

DR. KOZLOWSKI: Just to follow-up on that, you mentioned that you've never seen a correlation between bioassays and endpoint or marker. But you've always been dealing with new drugs so the question is could there be a situation where in the context of a drug already having had a lot of experience in the market and more being known about it, that that might not be the case, where a panel of bioassays may be more informative?

DR. NASHABEH: That will have then to assume that the other product is identical or basically equivalent to the primary product where the entire profile of product and process-related impurities are equivalent so that the clinical efficacy can be derived from this.

Also, another point that is quite important to mention is that biological characterization only measures an activity element. However, what's also equally important is to look

at the toxicity impact which is not measured by biological assays because they do not measure toxicity. They do not look at the mechanism of toxicity which is another key parameter in differentiating between a process, between a product-related substance and a product related impurity, and as such, I can give, for example, one of our products, Herceptin, for example, the cardio toxicity that is seen in Herceptin could never have been predicted by any of the animal studies, biological assays or the full characterization that we have done, and we have only seen this when we did the human clinical studies.

DR. VAN der Plas: Martijn Van der Plas, National Institute of Public Health from the Netherlands. I think we're missing a point here, namely that we're not basically trying to characterize protein. We are first of all going to compare it to something else because we're not talking about new proteins. We're talking about follow-on biologics or bio-similars or biogenerics or whatever word you like.

We know there are one or more originator's out there, and then you take your originator, you take your follow-on, or follow-on to be protein,

and then you're putting it through a number of tests which may or may not tell you whether it behaves itself in a certain system which may have certain relevance for the real biological situation.

I mean whether or not a bioassay is fully predictive, it's a gene report assay or a receptor binding assay, and you see that you have an original reference product and a new follow-on product, and that they are binding. Same thing you have an indication, okay, these are the same products. If they are different, then you know these products are no longer the same product, and sufficiently similar to claim a follow-on status, and then the company who wants to develop this protein has to decide what to do, but normally should go for a full clinical package or discontinue development.

So it's, I think the point of my

predecessor are valid, but they mainly relate to real new proteins and we should compare, should keep in mind these are not new products, and I think this point was also somewhat underestimated during the talks this morning. Everything revolves around comparisons, not about characterization.

DR. GERRARD: Terry Gerrard, TLG Consulting. The comment on bioassay is not reflective of toxicities, I mean that is certainly not their intent so that's certainly true for any protein, and I agree while bioassays are never predictive of efficacy, again they're an important part of your overall package of analytical comparisons between the innovator and the follow-on. And in the scheme of things, it's important to remember that while biological characterization is important, the ability of a bioassay to detect differences between the innovator and the follow-on is probably far below the other more sophisticated physical/chemical techniques.

So that the inherent variability of most

bioassays, it gives you basically a confirmation of activity, but probably isn't terribly useful at looking at true differences between two products.

MS. BROWN: When you actually do these comparative evaluations between two products, and you find them sufficiently similar in your biological characterization, and you find them sufficiently similar in all your physical/chemical characterization, would you say that a combination of those two things would justify a limited or reduced clinical testing program? Does anyone have any comments here?

MS. MUCHITSCH: Eva Muchitsch from Baxter. We have pretty good experience with this pyramid approach, do first a very extensive physical/chemical characterization of the proteins, and if there are some differences, you have always the questions what is the clinical relevance of these differences? So you have to go to the biological assays and if some previous speakers say they do not reflect the clinical situation, if you, for instance, go with a Factor 8 product in

hemophilic mice, you can, and you have two products, an old one and a follow-on product, and in this animal model, you can pretty well show, for instance, showing the effective correction of bleeding times.

So for me this is a perfect example if you have experience in this model and you can show efficacy in this relevant animal model, you can absolutely compare it with the follow-on proteins, whether you can see the same efficacious effect in this model or not.

And if you want to do, in addition, for instance, PK parameters in the same mice, you can also do comparison in the Cmax area under the curve. And if these are comparison and they match the biostatistical power, we want to see, for me there is no need to doubt that that will be the same in the clinical studies.

So if you have similarities shown, physical/chemical characteristic, then the next step, biological assays, and in very precise animal models there is much evidence that they are really

comparable because you have always to show the link is there really a clinical relevance about differences. If you see in the physical characterization one PK more, what does it mean? Okay. There is a difference, but how is that relevant? And if you show, for instance, that it is efficacious in the relevant animal model, it is comparable in PK parameters in an animal model, so for us, we have pretty good experiments that experience that you can rely on this data pretty well.

MS. BROWN: So are you saying that that would justify no clinical trials or limited clinical trials?

MS. MUCHITSCH: At least there is really a sound basis that there is no fear that you have at least limited clinical trials if you want or to go into humans in the late stage for pharmacovigilance or something like this. So with this parameter, you should be really safe that there is nothing that you haven't expected.

MS. BROWN: So basically what you're

saying is you're pretty safe on efficacy--also the other question of whether it is safe?

[No microphone for this portion.]

DR. KOZLOWSKI: Yes, so I guess the comment is for efficacy you would consider that sufficient, but clearly if you have another PK, that might make it--well that might make a difference for a safety parameter or for pharmacokinetics, and are you saying that PK in that animal model would also cover those issues?

MS. MUCHITSCH: Not only the PK. PK you will see only the comparability about the parameter. If you want to be safe and have one step further, but I think it is more a topic for pharmaco-toxicological characterization. Of course, I would propose to do also a good toxicity study in animals and there you will have also a very good comparison.

I think the point is really have the comparison. With a new product, no doubt you have to do all the studies including clinical, but with comparisons, there are a lot of data between, and I

would also propose to do a toxicity study as well to show is there, for instance, a mortality rate in the highest dose comparable with the old and the follow-on products?

DR. KOZLOWSKI: One other thing is you talked about proteins of different complexities. You've mentioned Factor 8 so that's probably a fairly complex protein. You should say that this should be across the board, because if you can do it for Factor 8, then you think that it would apply to everything.

MS. MUCHITSCH: I would think that the point is always to show it in the relevant animal model, and I think that that's the definition for that because if it's relevant, if you have experience in the development of this product, you can rely on this data.

MS. BROWN: Well, that kind of brings us to the end of first part of the question that says how can the clinical relevance of your functional biological assay like a binding assay or cell-proliferation assay be established? I mean

let's say that for the bioassay for the follow-on or the innovator, you just don't have access to it. You don't have access to their cell lines, whatever. How would you make that bridge?

MS. MUCHITSCH: I think that's also if you have a switch in the manufacturing process, you have to show data if they are comparable at the end, I think, and this standard should also apply to the comparison of an old and a follow-on product. I think that setting the same standard, you have to show it anyway.

MS. BROWN: Right, but for the actual bioassay--

MS. MUCHITSCH: Yes.

MS. BROWN: --where you don't have, you don't really have access to their bioassay, and there isn't like for human growth hormones, they've got the rat weight gain assay or the tibia width assay, where it's well established an in vivo model. But let's say there is an approved product out there, and you wanted to do a follow-on version of it, and the assay was not available, the

bioassay, and they've actually correlated the clinical relevance to like, let's say, a PD parameter during a clinical studies, so they've demonstrated that the bioassay has clinical relevance, but how would you propose to do that, let's say, with a limited clinical study? Would you propose to also do a PD assay to correlate that with an endpoint for your bioassay?

MS. MUCHITSCH: Well, I think this was my example of the, for instance, the bleeding time assay. If there are some relevant animal models you can rely on, I would agree with that.

DR. GERRARD: I think we're asking two different questions here. One is the clinical relevance of the bioassay, and the second is do you need to use the same bioassay as the innovator? And regarding the first one, as far as the clinical relevance, of course, it's always better to use a bioassay that has clinical relevance, but that's not always the case. We certainly in Europe and the U.S. have approved a number of products that we don't actually know the method of action so you

don't really know what's the most relevant bioassay, and I think Robin Thorpe alluded to that, you know, in beta interferon, some of the alpha interferons. We don't know the mechanism of action.

So that's something, that's a standard that we don't even do for innovator products, and as long as it works clinically, that's what matters.

And second, do you need to use the same bioassay as the innovator? Well, again, I'll go back to Robin's point. Yes, it's important to do a spectrum of biological characterization as part of your overall characterization of your product, but then you want to have, as your release test, the most rigorous sensitive and precise bioassay which may be different than what the innovator used.

MS. BROWN: I'm not saying that it should be the same as the innovator.

DR. GERRARD: Right. Just that it need not--

MS. BROWN: I'm saying that the follow-on

manufacturer would have to actually develop their own bioassay.

DR. GERRARD: Absolutely.

MS. BROWN: And does that need to be linked to any clinical relevance or can it be--because you've got to remember for innovator products, they actually do a clinical trial, and so if you do no clinical trial or a limited clinical trial, that correlation is going to be a little bit more difficult.

DR. GERRARD: But there's a lot of products for which there is no correlation, so--

DR. KOZLOWSKI: Mentioning that there are products were bioassays don't have correlation, I think as we move forward, there should be due diligence to look for clinical correlation. In other words, because in the past, they haven't been found doesn't mean that they should not be pursued.

DR. GERRARD: And sometimes it's obvious and sometimes it's always better to have one, but--

DR. KOZLOWSKI: And then a broader issue relates what you mentioned about the products where

the bioassay doesn't really link to the mechanism. So in some ways, that's potentially a more difficult situation because then you have an assay that may or may not relate to the mechanism in some way. There may not be a good alternative. Is there then an obligation to use the assay that was used because it was linked to the clinical studies?

DR. GERRARD: Well, I think you have to ask the general question then what's the importance of the bioassay as part of that product characterization, innovator or follow-on, and it just may not be relevant in either case.

DR. THORPE: Isn't it actually much more complicated than we're getting into here, because I think the Factor 8 is a really good example because although it's a very complicated or at least can be a very complicated large molecule, the actual assay is really an animal model, and what you're actually saying in the case that you've described so well is if I use the well-established animal model which has been around for years, and everybody knows how you do, it's a standard procedure, and I find the

same data.

Loads of companies over the last decade have done huge amounts of clinical work showing that that activity does relate on the clinical effect you want. So I don't have to do another trial. I'm relying on other people's trials. And that is the sort of true sort of follow-on route, isn't it? I think the issue of using bioassays to try and predict what's going to happen clinically is quite different and again doesn't relate to the complexity of the molecule because growth hormone is pretty difficult to do that well though it's much simpler is what I was going to say. Sorry for butting in.

MS. BROWN: No, no.

DR. KOZLOWSKI: Although just to mention complexity versus bioassays is that if you are not as comfortable with your ability to characterize the molecule, then it may put greater burden on the bioassay, not to say that complicated molecules don't have easier bioassays.

DR. MOLLERUP: But I think still that I

mean in order for a bioassay or an animal model to be so well established that efficacy, clinical efficacy data wouldn't be necessary, I'm not sure we've seen that quality of animal models yet.

DR. SHAW: Arthur Shaw, FDA. If I recall correctly, in the original description of this workshop, one of the charges was to use examples that could be generalized. And I want to kind of extend that, that examples, single examples where a bioassay is not predictive of a clinical or single examples where it is predictive should be always created with care if we're going to be generalizing.

Factor 8 is, in fact, not the best example. (A) it has a publicly available reference standard. It is a single deficiency protein, single protein deficiency that's been studied for a long time, so the complexity of the molecule is not what's relevant. It's actually the clinical situation and most of the bio recombinant proteins that we're dealing with are not designed to replace a deficiency. That's usually peculiar to the

coagulation products.

So one of the things that I heard was that there are so many examples where biological activity is not predictive of clinical that we really do have to be careful with it even when we have examples where it actually is predictive, that we can't generalize from that particular case.

This is not official FDA position.

[Laughter.]

DR. GARNICK: Rob Garnick, Genentech. I'm going to amplify a little bit on what the previous speaker just said. I don't think there are very many examples at all of which we've ever seen a relevance of a bioassay done in the laboratory to the clinical effect in man. I was struck by the fact that coagulation assays and even anticoagulation assays are probably some of the simpler ones for which actual reference standards exist, and I'll use TPA as another example of this.

By the way, TPA is a mixture of about 10,000 different isoforms, no one of which amounts to more than .1 percent of the total mass, and it

has very good and excellent bioassay which is a clot lysis assay which indeed is thought to be, in simple entomology, it's thought to be completely predictive of what happens in man.

In fact, all the chemistry has been very well known and elucidated for about 20 years. Nevertheless, it is not and never will be an nor should it ever be considered as a surrogate for a clinical trial in man because people don't react the same way as a laboratory plate. And that's an important to remember.

Many of the bioassays that are developed for innovator products and for follow-ons are going to be products of basically what science is available, what the company has available, and their sole purpose is to demonstrate functionality of that molecule. They're excellent tools for demonstrating consistency in the production process, but again, they have no relevance to clinical trials in man, and there is not a surrogate for such a trial.

Thank you.

DR. LUBINECKI: Tony Lubinecki, Centocor. I have two comments I'd like to make. The first is that while Factor 8 does have some advantages in

terms of validating a relationship between some of the bioassays and clinical parameters, I would also point out that most typically about a quarter of the patients who receive recombinant Factor 8s also have antibody responses, and so the bioassays certainly are not able to predict that with any accuracy.

The second comment is that when we are so lucky to have a validated bioassay with a validated relationship to a clinically important PK or PD or other parameter, that relationship is special. It isn't often attained and when it is and when it's validated, it's a very powerful thing, but when another product comes along that may or may not be similar to the first product, the bioassay for that validated product with a validated relationship is not available, and so it would be an assumption to think that the bioassay for the second product is related to clinical parameters without actually

directly testing it in the clinic for the second product and demonstrating that there is a validated relationship there also.

DR. MOLLERUP: I guess what you're stressing is the importance of not only generating all this data in those various models, but actually confirm that it also is what it is when we move into the clinic.

DR. VAN der PLAS: With regards to the remark of my predecessor that TPA may contain up to 10,000 isoforms in normal humans, to be provocative, I think this is irrelevant. What is relevant is the number of isoforms that is in the originator product. This is, again, when I was standing here the first time, I said it's all about comparison to a reference product. This is, in fact, the same case. We do not compare to analog, the human analog, now we compare to a reference marketed product, so follow-on products should be compared to a reference marketed product. These comparisons should be physical chemically show that it's highly comparable and then with the bioassays,

you should show that it has an identical biological activity, and then if you have this, you can indeed extrapolate, okay, it's looks like in this case TPA, it behaves like TPA in a bioassay. We do a PK/PD study in which we show that it is the same pharmacokinetic behavior as TPA, it is TPA, and let's approve it then.

I think this is the basis and then after that, if you've shown this, then everything that has to do with pharmacology an pharmacokinetics is covered.

The most important remaining problem then is safety and especially immunogenicity because nobody can tell you with real certainty what are the determining factors for immunogenicity.

Thank you.

MS. BROWN: So your position is that you do immunogenicity, PK, physical/chemical and biological characterization and no clinical studies?

DR. VAN der PLAS: That would be--well, of course, Europe we see the case-by-case approach,

and we use this as a kind of stop if we don't really know, so the actual approach should be case-by-case, but as I pointed out, I think this is a reasonable minimum requirement which should be, from a scientific viewpoint be satisfactory.

DR. MOLLERUP: Back to your first comment, I was a little bit confused over the difference you pointed out between comparison and characterization because basically it sounds to me like it's very much the same data you would be generating. Would you comment on that?

DR. VAN der PLAS: It's the same data. It's the same assays, but it's different goal. The goal for follow-on biologic, for a follow-on product or for a bio-similar product is to establish that it is highly comparable or almost the same or some semantic like that. So for this you need the comparison, comparison between a reference marketed product and a follow-on product, and there is, if you look at actual data, it's almost the same as characterization data, but the goal is somewhat different.

DR. MOLLERUP: The goal is not just to establish everything that you want to know about the product but also I mean, yes, how exactly how

do they compare, yeah?

DR. VAN der PLAS: You not only have to understand your own new product as you manufacture, but you also have to establish that it's highly comparable to something else.

DR. MOLLERUP: Uh-huh.

DR. KOZLOWSKI: Because that's a broader task actually, not an easier one. You have to characterize and compare. To follow up on the scenario you painted with TPA, so TPA has been stated to have a fairly good bioassay. Say a product did not have a bioassay that was equivalently good. Would you then say that you needed to show efficacy?

DR. VAN der PLAS: Well, it's case by case. I'd say that there are always bioassays. I would at least try to establish binding to receptor or some kind of interaction like that and then if you look at it scientifically and rather simply,

you can say, okay, if it binds to the receptor, then it will probably work, and if it has comparable pharmacokinetic, it will arrive at the right part of the body in the same way as the original product.

Okay. That's enough. That's the minimum, and then you don't need efficacy because efficacy can be extrapolated from your CMC and bioassay data together with the reference to the original product. This is, I agree, a little bit provocative, but this seems to be to me a valid minimum requirement.

DR. MOLLERUP: I guess back to the variation that you see in all these assays, this is in my mind a difference of your doing a whole efficacy study and confirming efficacy, what quality of biological characterization data would it take for you not to want to confirm efficacy in a clinical trial? In other words, when would you be sure that you had covered everything?

DR. VAN der PLAS: Well, do you want me to be provocative or--

[Laughter.]

DR. VAN der PLAS: Well, if you want me to be provocative, then efficacy is probably dependent

on the 90 or 95 percent of the main product. So if a follow-on product is 95 percent pure, and the original product is also about 95 percent pure as well, then it will probably have the same efficacy.

The real problem is not then the 90 or 95 percent main product which takes care of the efficacy, it's the remainder five to ten percent which may account for the safety. So this is just to be a little bit provocative but we should not get blind on complete similarity with regard to safety. Safety is probably rather straightforward. Excuse me. Efficacy is rather straightforward. Safety is the problem.

DR. MOLLERUP: Uh-huh.

MS. BROWN: Okay. I'd like to actually move on to the second question that was printed in your brochure. Is there another question? Oh, I'm sorry.

DR. CLAUSE: Kathleen Clause, FDA. One

thing that really hasn't been emphasized enough is that even in the best of the validated bioassays, you seldom get one that is so predictive of the activity of the molecule or that has acceptance criteria that are narrow enough to be consistently useful. So I think that the possibility of taking a follow-on or two products made by different manufacturers and consistently coming up with one being let's say consistently less potent than the other, to the same degree, over and over again, is going to be extremely difficult to achieve given the limitations of the majority of the bioassays and given the fact that in many instances we don't know the mechanism of action.

So I think taking that into consideration, and you can fall back on the case-by-case basis, unless you do have an extremely good bioassay that has a very long history of reliability and very tight criteria, I think that they're going to be some degree of limited utility, limited predictive value or consistently predictive value, and you will always need additional studies.

DR. MOLLERUP: I guess one final question that also needs to be considered because one is absolutely, I agree, important parameter is product

purity, but I think another one again if we move between various host cell systems, then post-translational modifications may nor may not be reflected in those assays and I think that needs to be taken into account as well.

MS. BROWN: Okay. Let's move on. I think we have to limit our time for question number two so we can have enough time to do question number three, but number two is what are the appropriate standards for comparison of biological activities?

And I think this is particularly interesting for me because if there is no international reference standard, if there is no USP standard or European pharmacopeia standard, you're limited to go and collect some of the innovator's product, and I was actually talking with one of my colleagues outside, and he said how do you choose the product, or the innovator product, how do you know you're getting three drug

substance lots because you wanted to make sure that you capture all the variability of the manufacturer because different lots of drug product can be made with identically the same drug substance.

I mean you would never know, right. Only the innovator would know how they actually manufacture that. And not only that is that you have to separate the excipients, the formulation excipients away from the product. I mean that the follow on protein manufacturer could potentially remove impurities. It could change the activity of the product, and so I mean this particular question, I think, is very provocative, particularly for products that don't have an existing reference standard.

DR. NASHABEH: The true comparator is innovator in-house reference standards which is linked to the clinical safety and efficacy.

DR. KOZLOWSKI: To have follow-up on that, so obviously the reference standard may not be available. So the question is if one looked at, you know, ten drug product lots, 20, 30, at some

point, in other words, is there some number, assuming that one can purify the drug substance without a lot of complex steps, because Robin Thorpe mentioned clearly you can change the product by purifying it. What would be enough to compare, as this sort of makeshift standard?

DR. NASHABEH: Actually, the drug substance, not the drug product, is the true comparator because that's where your process-- that's reflective of the process variability of the drug. The drug product is further processed from the drug substance. And of course some of the points that when you get a drug product, you don't know whether these are derived from the same drug substance or not.

In addition, the drug product may have already undergone some degradation upon storage, handling, so they may not have reflected the actual state of the true reference at the time of manufacture. So there are--

DR. KOZLOWSKI: But to take the argument theoretically, say you have a drug product that's

aqueous formulation so the generation of the active pharmaceutical ingredient for that drug product does not involve significant manipulations. Clearly, you can have some change based on degradation, but if you use those values to set your lower limits in stability so you're not working within a range of degradation that the innovator product, you know, doesn't occur during clinical use, so again is that also problematic?

DR. NASHABEH: Assuming you know all the relevant degradation pathways, which require significant understanding of how the product works and how the manufacturing because some of these are also related to the manufacturing process itself, which is typically information that are not in the public domain and cannot be easy to obtain and require a lot of investment in actually deriving what, how the degradation pathways are.

So assuming you know all the degradation pathways, you can back calculate what the actual material is and then you have enough lots that you could pull together. I think in all these cases

what this will give you is a representation of a window of the manufacturing process. It will not truly give you a reflection of what the material was in the clinical program which is the basis, according to ICH Q6B, in terms of establishing actually product specifications.

DR. KOZLOWSKI: Again, sort of to be provocative, in theory when you release those drug lots to the market, you're assuming that they're close enough to the reference standard which is linked to the clinic from the innovator perspective to allow them to be released. So, you know, granted, it's a comparison to a comparison and maybe that fails, but nonetheless, the innovator themselves relies on that relationship.

DR. NASHABEH: When you release them, they are an acceptable range. But they're not within range.

DR. BORDENS: Hi. Ron Bordens, Scherring Plough Research Institute. I just wanted to address your comment. If you compare to something that may be degrading, it's almost like a copy of a

copy of a copy that by the time you get to the third generation, you're going to have nothing like the original, and I think we found a lot of that in the interferon standardization process that we did in the '90s that, you know, clearly, it was a discontinuity of calibration because of different preparations.

So you know, follow-on products really would have to go back to the original molecule to be absolutely follow-on, I think.

DR. SCHENERMAN: This is Mark Schenerman from MedImmune. I think it's also important with regard to reference standard to recognize that the innovator may apply different acceptability criteria to the reference standard than to the drug substance or the drug product. Typically, there might be tighter criteria for the reference standard and that is usually proprietary. So how tight that needs to be is based on years of clinical and manufacturing experience.

DR. MOLLERUP: Back to the issue of variability that Robin also talked about and was

mentioned this morning, I mean you have the variability of the innovator product. You have the variability of the follow-on, and the challenge here is to figure out how can you actually link these together maybe based on one or two data points, and I think that's extremely challenging.

DR. GARNICK: Rob Garnick, Genentech. I just want to add a couple other points to what some of the groups said. The proper reference, and by the way, these are reference materials, not reference standards. The standard according to even ICH must be defined as a substance that's been qualified in basically a reference laboratory, official laboratories. I'm thinking of WHO or NIH standards, NIBSC standards. These are all reference materials by definition.

So let's make sure we're talking about the same thing. On top of that, the issues of degradation will affect or a drug product--a reference material isolated from a drug product will undoubtedly be affected by the effects of degradation of the product, and I'll point out one

other thing, and that is if you remember, I think Robin does, the International Study for Growth Hormone, the reference standard, we were all issued vials of material and about seven or eight referenced labs tried to determine just the amount of active drug that was in those particular vials.

And if memory serves, there was about a 20 to 25 percent variation in just trying to determine the protein content of that particular vial, and that would have a tremendous effect on how a company would determine the dosing of a product if they got the amount in the reference wrong. And it's very easy to do, and it's not trivial.

Thank you.

DR. THORPE: I can certainly confirm it's not trivial, and there are lots of examples like that one, and in fact, even worse. And I think it is somewhat of a myth that people think that the volatile activity and the bioassays are inherently variable, and that if you're going to do something like an immunoassay, it's going to be much tighter, actually completely wrong. Usually it turns out to

be the other way around because the people that do bioassays, at least people in the pharmaceutical industry that do bioassays are usually very, very careful because they know they've got problems, whereas they think immunoassays are easy, and they're not.

So you do have to be very, very careful, but I think these are all technical challenges. I'm not saying, I don't think they're necessarily insurmountable, but they're certainly very important and need to be carefully addressed.

And while I've got this I thought I should also point out something that was said earlier that you can use receptor binding assays as kind of surrogate bioassays, that's not usually the case. You'd be able to demonstrate very good receptor binding for incorrectly glycosylated or even non-glycosylated EPQ, which would be completely inactive in real bioassays and certainly inactive clinically. So I think you have to be very, very careful what you call a bioassay as well in this kind of scenario.

MS. BROWN: Since we don't have any more comment--is there any more comment for No. 2? Okay. Let's move on to question No. 3: Based on

the biological characteristics, how can product related impurities be distinguished from product related substances and the desired product?

If a product related substance can be identified and distinguished, should the acceptance criteria be different for the follow-on product than what is observed for the reference product?

I can give you an example. For example, what if the innovator product had a level of a product-related substance of ten percent, and the follow-on manufacturer came in and they have a level of 15 percent. Should it always be at least or not to exceed what the innovator product's levels are for their impurities and product-related substances?

Or for product-related substances that actually have activity, would you have a different standard for that? For example, would you allow a

little bit more for that particular variant?

DR. NASHABEH: That would be good if it applies to the innovator product. Again, the acceptance criteria by ICH Q6B cannot be strictly define based, whether a parameter is proprietary substance or a proprietary impurity. It definitely, it makes a difference whether it's substance or impurity, but in setting acceptance criteria, one has to look also at the preclinical and clinical experience because these are the predominant factors that goes into setting specifications. So we cannot divide the acceptance criteria from the clinical experience with a given product in terms of setting it.

And also going back to the concept of product-related substance and product-related impurity, again quoting from ICH Q6B, "the element of activity is only a component in differentiating whether it is a substance or an impurity."

The other two factors are basically efficacy and safety, so without establishing that a given variant has no impact on safety one cannot

make the differentiation whether it's substance or an impurity.

So the biological characterization by itself is not sufficient to make a distinction whether a variant is a substance or an impurity. You have also to rely on the clinical and pre-clinical experience to add to that knowledge in order to make the differentiation. This is a process that we go through in terms of classifying a variant, whether it's substance or impurity, so we have to rely not only on the biological characterization but also on the knowledge that we obtain from the clinical experience.

You may have examples where a parameter can be fully active like variation in sciatic acid, but can have a significant impact on pharmacokinetics. That may actually lead to classifying a given variation as an impurity versus substance, not because of biological activity but because of other implications. So again we're only looking at one facet of the differentiation between substance and impurity.

MS. BROWN: But the actual innovator would have done their clinical studies and you would have done some comparative characterization, identified

that level of impurity or product-related substance, and would you, because you've done comparative characterization with the innovator and they've done the clinical study, you know, the safety, I shouldn't say really safety, but the efficacy has been demonstrated.

DR. NASHABEH: I know this is not the topic of this session. It's going on in Panel A, but the assumption that you can do a comparative, complete comparative characterization to elucidate the product variants between an innovator and a follow-on without full access to the methods that enable this analysis and the critical reagents is really a myth because any true comparison has to be based on knowing what to look for, which are critical attributes that you can only obtain through our continuous knowledge that we gain through clinical development and understanding what is relevant of a given molecule to track and

monitor for.

We also develop assays that are critical and specific to certain elements that we know that are relevant from our clinical experience and pre-clinical studies. So the assays that are developed are specific to certain aspects that we know are critical. Without that knowledge, you're basically taking a complex molecule and trying to just profile it without knowing what is relevant to profile and you end up with thousands of parameters with no true indicator of what is really critical to actually assess.

So without that knowledge a true comparative characterization cannot be performed.

DR. KOZLOWSKI: As kind of a follow-up to that, in meetings where innovators discuss specifications, the question of clinically relevant specifications always comes up. What attributes really matter?

And it seems to me that in many of these meetings, the view is we really have very few attributes that we define in a real way as being

clinically relevant or not. It's obviously a goal we'd like to achieve. So the question really is when you say these parameters based on in-house knowledge are known really to be product-related substances, is this a lot of the different variants that you see? In other words, how much of this information really exists in the hands of the innovator to begin with?

DR. NASHABEH: I mean there are several examples that we are aware of. For example, definitely glycosylation as related to clearance. Glycosylation at times as it relates to effective function. Some either clipping or aggregation and again because we have assessed, we have obtained the clinical efficacy and safety from the clinical program, we understand that the product mix as we manufacture it be a defined process, giving us a distribution that we can profile and characterize to a certain extent, we can say with certainty that distribution of variants that we have is safe based on the clinical trials we have.

Now, once you move to a different process,

that will then inherently have different variants and different impurities, that correlation cannot be then extrapolated from the innovator clinical studies because since--this is exactly the point because we cannot link what parameters have direct clinical implication or not so we rely on the totality of the profile that we have.

We can say that with a given profile, with given methods, with given variations, we know that this combination has proven safety and efficacy manufactured by a given process and under controls.

DR. LUBINECKI: Tony Lubinecki, Centocor. I would agree with all the comments from the previous speaker and add that one set of specifications is linked to one product from one process with one clinical and non-clinical history, and it's not possible to apply the specifications or standards from one product to another product. It doesn't have that same exact family of processes, clinical history and non-clinical history.

DR. SIEGEL: Rich Siegel, Centocor. Just

following up a little bit on Tony's comment. You know one of the chief impurities that we see related to host cell proteins, and this is a complex set of materials that's very specific to the cell substrate as well as for the media that's used, and it's defined by a proprietary usually amino assay the result being a specification based upon you know parts per million or something like that, and the key is that specification is clinically validated, and by comparing that result to a follow-on with the same number has absolutely no meaning, and this is a critical point relative to safety.

The definition of these materials is typically not well understood and if it did have adjunct-like effects, it could be disaster for the patient.

MS. BROWN: So are you saying that like for a host cell protein could affect the efficacy?

DR. SIEGEL: No, what I'm saying is it could easily affect safety.

MS. BROWN: Okay. For immunogenicity?

DR. SIEGEL: Immunogenicity, certainly, yes.

MS. BROWN: Okay. So assuming that the

follow-on manufacturer would come up with their own impurity profiles, they've developed their own assays, they've come up with their own biological assays, and they have done clinical immunogenicities, PK studies, physical, chemical and biological characterization, in your opinion would that be adequate?

DR. SIEGEL: No, because the whole point of something like a host cell assay is it's clinically validated, and that requires treating a large number of patients, typically many more than required for efficacy.

DR. GERRARD: It's important to remember that impurities generally do not cause adverse events, that many of the therapeutic proteins can have adverse events, in fact, some very, very severe, but in only very rare cases, and that's associated with aggregation, they're not associated with adverse events.

In regards to your first question, as far as it's certainly important for the innovator and for follow-on to characterize process impurities from product variants. That would be expected for any therapeutic protein.

It's expected that a follow-on because the

process is different probably would have process impurities that are different. But nowadays we're talking about proteins that are so pure, the question is once you get below a certain percent, does that matter? And I think you can ask the question about the effect of product variance by doing PK studies, and if you have similar PK, you may not need to go any further.

MS. BROWN: But how would you know whether a certain level would not matter? I mean what is that level?

DR. GERRARD: Well, but that's not a unique issue for proteins. We face that when you look at drugs as well. I mean there are impurities in drugs.

MS. BROWN: But we have a clinical trial.

DR. GERRARD: And I think you have to ask at what point I mean you characterize anything at the one percent level, .5 percent level.

MS. BROWN: But that's characterization. I mean what you are saying is that the level of these impurities may not have any clinical consequence.

DR. GERRARD: Right. That's generally what's been observed in therapeutic protein.

Therapeutic proteins do have adverse events, but it is due to the inherent pharmacology of the protein and not due to impurities.

DR. GARNICK: Rob Garnick, Genentech. I'm not sure I buy that. I don't know that any of us has the fact that says that because many of these biological products have pleiotropic activities, we don't know what the toxicities are linked to. We don't know that some of these impurities that makes this at 1, 5, 10 or 15 percent level don't have tremendous physiological activities.

A good example, we have the drug Herceptin which is probably one of the best examples of a

well-designed molecule. We know what it does fundamentally and we don't exactly know the complete mechanism of action, but we know Her-2 receptor binding is involved. There's a diagnostic for this molecule. It's pretty well understood.

We have no understanding of why cardio-toxicity occurs with that drug and I rather, you know, I'm not sure that I believe that it's not a process related purity or anything like that. We have no knowledge whatsoever. And to think we do I think is really the precipice that we could easily fall off, convincing ourselves that things are easy when they're really not.

And we need to be very, very careful about that. One other point is that very few of these molecules are actually pure in any analytical sense of the matter. These are complex mixtures. Most of these products are not in any analytical sense very highly purified at all. What we know is that we can produce a consistent mixture of these processes, starting with a known cell line and a known recovery process.

The minute you vary from that particular recipe, and again I guess Tony made it, the product, the process, the specifications, the

assays are all, very intimately linked. Once you move away from that, all bets are really off, and the consequences are very different--not so much from an efficacy standpoint, but from a safety standpoint, are really difficult to ascertain until you go into very large patient populations.

And unfortunately, for follow-ons, I think all said and done, we probably will never have materials which are absolutely identical to the innovator's product. They will be different in some way, shape or form. And then to not be able to rely on characterization, followed by bioassays and PK/PD and not do clinical trials is really asking for some serious results, and unfortunately the patients and public will pay for it.

MS. BROWN: Well, okay, let's say not full clinical trial, how about an abbreviated clinical trial, based upon the knowledge that the drug has actually been out on the market, I mean the

profile, the mechanism of action is known? I mean how can you justify a full clinical study when there is so much--

DR. GARNICK: I don't think we're justifying. We're not suggesting full clinical trials, but I think, in my actual opinion, I think we need to really concentrate on the concerns about efficacy and what we know about these molecules and their toxicities so that we can at least have the confidence, the public and the patients can have the confidence that what they get will actually reproduce or be similar to what the innovator produced and that we don't have some new experiences like we're finding with Vioxin of the Cox-2 inhibitors now that are having tremendous effects on the industry and on the FDA.

MS. BROWN: Thank you.

DR. GARNICK: Thank you.

MS. STEIN: Katie Stein, Macrogenics. I don't have any examples specifically from our own products, but I would like to elaborate on what has been discussed in the last couple of minutes, and

that is that most of the proteins that we're dealing with are complex proteins that have micro-heterogeneity.

And nobody has really separated all these various microforms to look at the biological activity of each microform so that the bioassay that one uses is, in fact, the product of all of the microforms that are product related generally in the product, and most of the characterization that's being done to determine these microforms is really done on the drug substance at a concentrated level, and I would posit that a follow-on manufacturer doesn't have access to the drug substance and so you have to deal with a final formulated drug product.

And I guess I would just ask the audience whether one can elaborate on some examples where you think that the drug product is sufficient to do this kind of biological characterization or whether one really needs concentrated drug substance, where most of the characterization is done?

DR. VAN der PLAS: Thank you. I would

like to turn this point around, also for the audience. The actual patient will not be treated with the drug substance. He or she will be treated with the drug product. So you can also argue the other way around. The only thing that really matters is the drug product because that's what is going into the patient.

MS. MUCHITSCH: I have also some comments regarding impurities. I think you should keep the same acceptance criteria. Like I pointed out previously, if there is a change in the manufacturing process, that could be also achieved in the impurity for instance.

And in that case, I would suggest to do what you would apply to a new product, do an extensive toxicological risk assessment either by literature or if it's not available or if there are no data by toxicity studies in animals because usually you don't think, for instance, if there is no doubt that the protein per se is toxic, maybe the impurities are toxic, and therefore I would suggest to do also toxicity studies in this case.

MS. BROWN: Do you think we could focus on this first question: Based upon the biological characteristics, how would a follow-on manufacturer

determine produce related impurities from product related substances?

DR. KOZLOWSKI: I think so far we've heard a lot of comments that you really can't determine product related substances from impurities with a bioassay. I haven't heard anybody comment on the fact that, sort of the opposite side, that if, in fact, you could somehow with a bioassay or a series of bioassays look at some of your impurities and characterize that they behave similar to the innovator, is there anybody who thinks they would be treated differently because of that?

MS. BROWN: Okay. Let's see. Did anybody actually have any comments to what was--you probably didn't read it--what was actually put on the screen? And actually tomorrow morning, we're going to summarize some of the conclusions that we had here, where consensus is reached. We're all represented today and we're going to summarize

everything and present it tomorrow morning, and with the results of each of the breakout sessions.

DR. KOZLOWSKI: Of course, that's not an official--right--there will be an official transcription independent. I was just wondering since I guess we have a couple of minutes left--one of the issues we talked about was standards, and it seems to me there were a number of opinions about the importance of actually getting drug substance in order to do these comparisons. We also heard some comments about the fact that drug product is the most important.

Anybody want to comment under what circumstances they think drug product could ever be used, I guess not as a reference standard--we stand corrected--as a reference substance?

Actually I know you kind of talked drug product is fine. Do we have anybody else? Because I think we want to get other opinions too. I mean you can comment also, but just because I think it's a critical question, what will be the comparator, and if there are views about circumstances when a

comparator could be obtained? Sort of simply from purchasing product off the shelf or is that--does nobody think that that's a viable option any cases?

DR. SCHENERMAN: Mark Schenerman from MedImmune. I think typically the drug substance goes through a very intensive characterization process and it's a little easier to understand the subtleties of the interactions between all the assays on drug substance where there is no potential interferences with excipients from the drug product. So I think it's a little bit more straightforward approach, at least from the innovator point of view to use that as a reference material, I guess is the right terminology.

DR. VAN der PLAS: Well, that's really the interesting point because it's probably the interference of the excipients that caused, for example, eprex [?] to cause PRCA. Nobody knows what's causing PRCA, but it happens after albumin was removed from the formulation. So apparently this interaction was important and it underscores the importance of the drug product, and maybe this

is my European standpoint, that at least we would not talk legal issues today, but the European is radically on the fact that when you want a bio-similar product, then it's a bio-similar drug product. So the bio-similar drug product is at least from a legal viewpoint the only thing that matters.

Yes, well, not as American, I would like to emphasize again that everything that I've said here is personal.

MS. BROWN: You actually said how important it is to actually analyze the drug product and not the drug substance, but there is a possibility that this separation of excipients can increase the degradation profile, and in fact the drug product that has been modified this way to get enough of it to do your analysis is really not representative of the innovator's product at all.

And so can you comment on that at all?

DR. VAN der PLAS: Well, only theoretically, but in theory, the follow-on manufacturer could formulate product and then

extract the drug substance so that he validates the method. That's a scientifically sound method, I believe.

MS. BROWN: So you would actually separate the excipients and then reformulate it according to what the follow-on manufacturer intends?

DR. VAN der PLAS: No, you have an original drug product and you have your follow-on drug substance. You formulate it and then you both deformulate them.

DR. MOLLERUP: So you work backwards in both cases?

DR. VAN der PLAS: Yes, and then you have--well, it's not the perfect method, but at least it's identical in both ways, both cases.

DR. GARNICK: Rob Garnick, Genentech. It's important to think back to where this all started. For small molecules, I think the approach that your companies used is to actually isolate the active drug substance from the final product and to use that, actually use multiple batches and try and characterize those. And that's fine for a small

molecule because you have a molecule that, you know, is pretty well defined. The impurities are well understood.

It can be characterized completely. It's usually extremely pure. Typically 90--I mean the specifications are always 90 to 100 percent, 110 percent. So you can do that for small molecules. You can't do this for proteins. Okay. As most of you know, our formulation processes occur in process. The product isn't isolated as a pure API like is done for small molecules and then reformulated. These are done in process and the reason for that is stability.

We do that to ensure that the drug substance is formulated effectively so it typically can be filled into final product. To try and isolate them, many of them are extremely labile. You're going to have oxidative processes, the oeamidation going on, aggregation, you name it. What you're going to wind up with is something that you're now going to call a reference material which will probably have little or no bearing on what the

innovator's actual reference material actually was.

So this is--in pure analytical chemist's statement, this is the wrong way to go. We were all trained not to do this in the universities. Why are we doing this now? This is not the appropriate approach.

The true reference material for any follow-on has got to be the manufacturer's reference material. There's just no other substitute.

DR. KOZLOWSKI: Again, just to push this point. I'm taking the stability and degradation into account, but say you have a product and there are products where the bulk drug substance is actually in the same buffer that it's formulated in, and all you're doing is filling it, and that's the only difference.

So in such a case, do you think that's also a problem?

DR. GARNICK: Again, to try and isolate the material without going into exactly the same buffer system, the same excipients, the same

contact with container closure components, you just can't get there from here.

DR. SCHREITMUELLER: Thomas Schreitmueller of Hoffmann-La Roche, Switzerland. I also would like to elaborate a little bit on what was said before. I think in principle it cannot be validated if you re-isolate from final formulation the protein in there that you really recover everything. For example, let's talk about host cell proteins. You have a very broad spectrum of different proteins with different properties. How would you be able to ensure that you really recover everything, what is in the originator's product, and I think the same holds also true for product related impurities. I think this process in principle you cannot validate.

DR. KOZLOWSKI: Let me ask you the same question. What if in fact your bulk drug substance that's used as drug substance is in the same buffer and the whole conversion to drug product is simply the filling line?

DR. SCHREITMUELLER: Okay. Here you very

often face the fact that you do the testing even not as the final drug substance stage but rather then some steps before where you have more easy access to those proteins.

MS. BROWN: Well, it looks like we've used up all of our time so I'll let you enjoy the break before the next breakout session. Thank you for all your participation.

[Applause.]

[Whereupon, at 3:00 p.m., the breakout session was concluded.]

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